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RADIATION INDUCED CHANGES IN INTRACRANIAL PRESSURE AND ARTERIAL BLOOD PRESSURE

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Twenty Macaca mulatta monkeys were exposed to cobalt-60 gamma radiation at the rate of 1000 rad/minute for mid-thoracic doses of approximately 1307 rad to 10 monkeys and 2244 rad to the remaining 10 animals.

The average intracranial pressure increased in both groups following exposure, but the response observed in the low-dose group was not so great as that elicited in the monkeys that were exposed to higher levels of irradiation. Hypotension developed in the majority of animals postirradiation, and the degree of response was greatest in the high-dose group of monkeys.

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Editorial Review by Lt Colonel W. A. Belford, Jr.
Department of English and Fine Arts
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This research report is presented as a competent treatment of the subject, worthy of publication. The United States Air Force Academy vouches for the quality of the research, without necessarily endorsing the opinions and conclusions of the author.

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CERTIFICATE

The animals involved in this study were maintained in accordance with the "Guide For Laboratory Animal Facilities and Care" as published by the National Academy of Sciences, National Research Council.

John W. Watters, Major, USAF, VC

INTRODUCTION

Many of the symptoms which follow high doses of radiation have been attributed to increased cerebrospinal fluid pressure[1]. Herniation of the brain through the foramen magnum has been observed in monkeys dying between 6 and 55 hours following 4500-6000 R of x-irradiation to the head, and moderate edema was seen in the brains of animals receiving 3000 R[2]. A study of human patients demonstrated that changes in cerebrospinal fluid pressure had no direct effect on cerebral function, possibly because there are no absolute pressure receptors in the human brain[3]. It was concluded that when symptoms of cerebral dysfunction are associated with a change in cerebrospinal fluid pressure, the association results from the effect of factors common to both the pressure and the dysfunction. No abnormal elevation in CSF pressure was observed in 20 mongrel dogs that had been exposed to 1000-4000 R x-irradiation to the head only[4].

The head exposure of rats to 10,000 R of x-irradiation produced only subtle changes in the permeability properties of the blood brain

1. P. Bailey Intracranial tumors (Springfield, Ill. 2nd Ed., Charles C. Thomas, 1948).

2. J.A.T. Ross, S.R. Leavitt, E.A. Holst, and C.D. Clemente, Neurological and EEG effects of x-irradiation of the head of monkeys. Arch. Neurol. & Psychiat. (1954) p.238.

3. H.W. Ryder, A. Rosenauer, E.J. Penka, F.F. Espey, and J.P. Evans. Failure of abnormal cerebrospinal fluid pressure to influence cerebral function. Arch. Neurol. & Psychiat. 70 (1953) p.563.

4. D.E. Redmond, Jr., R.H. Rinderknecht, and P.T. Hudgins. The effects of total-brain irradiation on cerebrospinal fluid pressure. Radiol. (1967) p.727.

barrier[5] while other investigators have reported that the reaction of the cerebral blood vessels to ionizing radiation in monkeys is characterized by blood vessel fragility, brain edema, and general vasculitis[6]. Circulatory disturbances which result in increased capillary permeability and protein leakage in some instances initiates edema and in most cases aggravates or perpetuates it[7]. The whole-body exposure of monkeys to x-irradiation has been shown to produce a precepitous drop in blood pressure a few minutes postexposure, and transient performance decrement has also been demonstrated during this time period[8]. Since it has been shown in baboons that intracranial pressure changes induced by certain drugs may be much longer lasting than blood pressure changes[9], this study was initiated to monitor the subdural pressure and the systemic blood pressure following whole-body irradiation in an effort to establish a possible physiologic cause of transient incapacitation induced by supralethal doses of gamma irradiation.

5. V. Nair and L.S. Rothe. Effects of x-irradiation and certain other treatments on blood brain barrier permeability. Radiat. Res. 23 (1964) p.249.

6. C.D. Clemente, J.N. Yamazaki, L.R. Bennett, P.A. McFall and E.H. Maynard. The effects of ionizing x-irradiation on the adult and immature mammalian brain. Proc. Intern. Conf. Peaceful Uses Atomic Energy, 2nd, Geneva 22 (1958) p.282.

7. A.E. Richardson, Some clinical aspects of cerebral edema. Proc. Royal Soc. Med. 58 (1965) p.604.

8. P.H. Chapman, Behavioral and circulatory responses to x-irradiation delivered at 200 rads per minute to whole body and trunk only. SAM-TR-68-111, (September 1968).

9. S.J. Corne, R.J. Stephens, and L. Symon. The effects of drugs on the intracranial pressure of baboons. British Pharmacol. Soc. 34 (1968) p.212.

MATERIALS AND METHODS

Twenty monkeys (Macaca mulatta) of either sex, weighing 2.5 - 4.0 kg were anesthetized with phencyclidine HCl (2mg/kg) and pentobarbital sodium (20 mg/kg). A 5 mm hole was trephined lateral to the midline in the skull, and threads were tapped for the plug shown in Figure 1. The dura was incised, and a polyethylene tube, Figure 2, which had been shaped to a 90° angle and perforated along two sides, was placed beneath the dura. The Teflon plug was screwed tightly into place, and the retaining plug was tightened firmly against the silastic gasket. The polyethylene catheters were filled with physiologic saline solution prior to implantation, and a small bore water monometer was filled to 12 cm. of water and connected to the catheter adapter until the ICP stabilized. The femoral arteries were catheterized with 0.027" I.D. Intracaths (C.R. Bard, Inc., Murray Hill, N.J.) for monitoring the systemic blood pressure.

The intracranial catheter was attached to a venous transducer (Statham Model Nr. P23AA), and the pressure signals were recorded on a 6-channel Dynograph (Beckman Instrument, Inc., Chicago, Illinois).

Ten of the monkeys were exposed to cobalt-60 gamma radiation at the rate of 1,000 rad/minute for an average mid-thoracic dose of approximately 1307 rad. The remaining 10 monkeys were exposed at the same rate for an average dose of 2244 rad. All of the animals were irradiated in left-lateral recumbency with the cobalt source above the right side. The cobalt-60 irradiation facility has been described elsewhere[10]. Each monkey had 2 dosimeters (Harshaw Type 700 LiF) attached to the thorax for measurement of entry and exit doses. These doses are listed in Table V.

10. K.A. Hardy, H.A.W. Spetzler, R.W. Cockran. The SAM high-level cobalt-60 irradiation facility. SAM-TR-65-65, (September 1965).

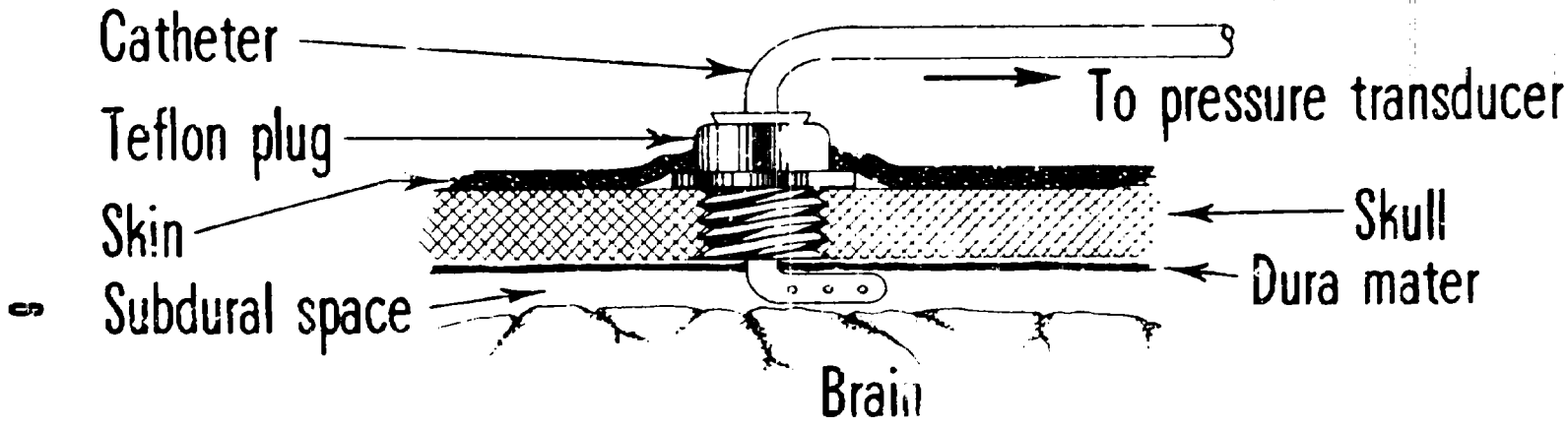

FIGURE 1—Cross-section illustration of Teflon plug and subdural catheter placement.

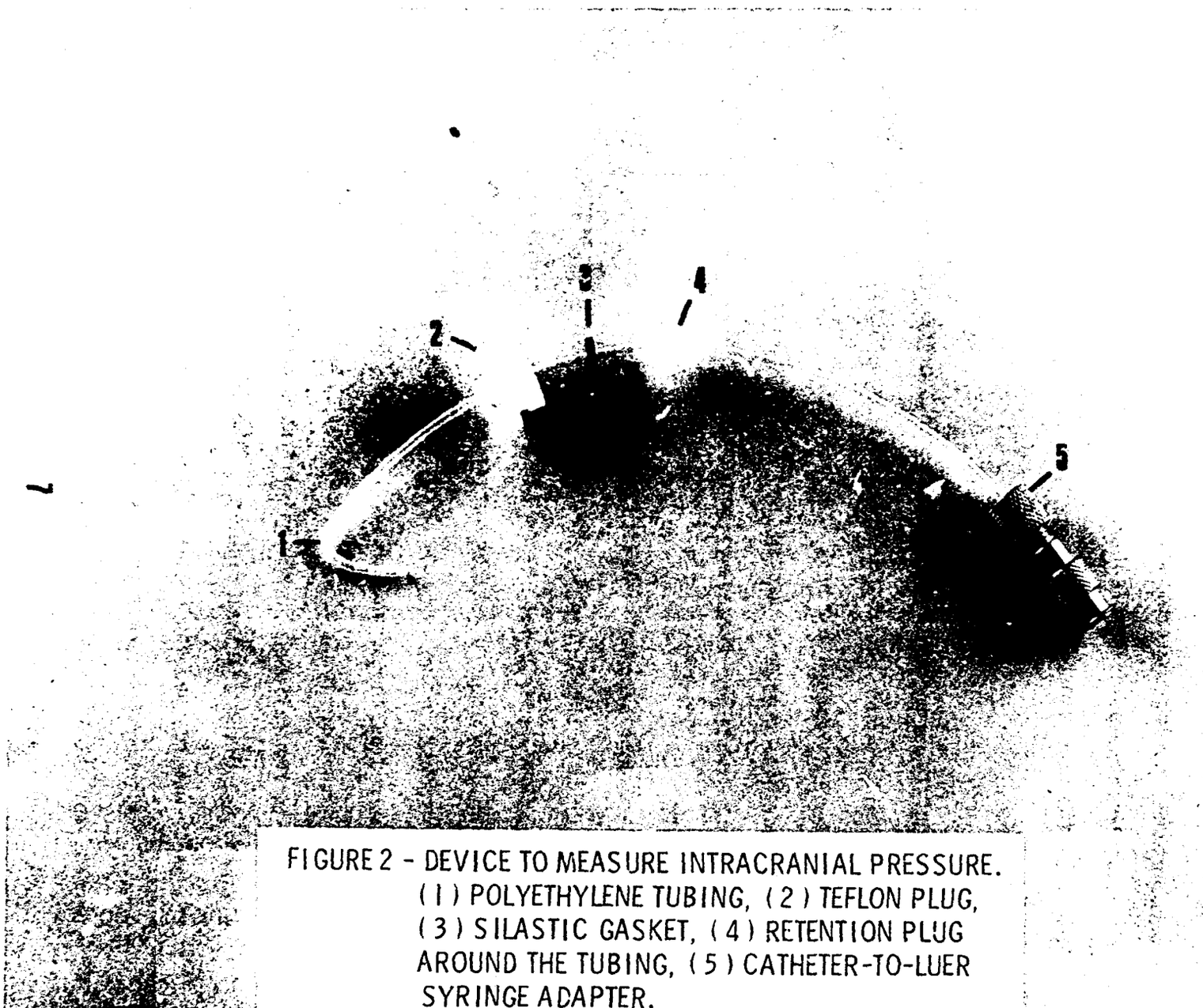

FIGURE 2 - DEVICE TO MEASURE INTRACRANIAL PRESSURE. (1) POLYETHYLENE TUBING, (2) TEFLON PLUG, (3) SILASTIC GASKET, (4) RETENTION PLUG AROUND THE TUBING, (5) CATHETER-TO-LUER SYRINGE ADAPTER.

The intracranial and arterial pressures were monitored for approximately 45 minutes prior to irradiation or until both pressures were stabilized and the levels of anesthesia were correct. The pressures were recorded during the exposure and for a period of 90-minutes post-irradiation. The postexposure times were expressed as time from the start of the exposure period.

RESULTS

Cobalt-60 gamma irradiation induced an average increase in the intracranial pressure beginning approximately 3 minutes after initiation of irradiation and reached the peak in 6-7 minutes. Tables 1 and 2 list the intracranial pressure readings for each individual monkey, and figures 3 and 4 illustrate the average response of the intracranial pressure to irradiation.

The low-dose group of primates exhibited slower and less extensive rise in ICP than the high-dose group, and the declining pressure did not exhibit the very slight fall below the established baseline as was noted in the high-dose group. Another variation between the 2 groups was that maximum response in the low-dose group was seen at 40-minute postexposure which appeared as the second peak of a bimodal response.

The high-dose group of monkeys demonstrated a rapid and marked increase in ICP followed by an insignificant decrease which extended slightly below the original baseline. The ICP began a gradual rise after the nadir was reached and continued upward until the end of the recording period. Although the pressures fluctuated throughout the monitoring period, and the individual responses differed, pressures were significantly higher at the end of the 90-minute observation period.

TABLE I

INTRACRANIAL PRESSURE OF THE LOW-DOSE GROUP

Monkey No.	1	2	3	4	5	6	7	8	9	10	Mean	S.E.
Pre-exposure Pressure ($cm\ H_2O$)	8.0	11.0	8.5	6.0	12.0	11.0	9.5	12.0	6.5	6.5	9.1	
Minutes Postexposure	Percentage of Pre-exposure Pressure											
1	100	100	100	100	100	100	100	100	100	100	100	0.0
2	100	100	94	100	100	100	100	100	100	100	99	0.6
3	100	104	94	100	108	100	105	100	111	107	103	1.6
4	100	104	100	100	108	105	105	104	115	107	105	1.4
5	100	104	111	100	112	114	105	117	115	115	109	2.0
6	106	100	123	100	116	118	105	117	115	115	112	2.6
7	106	95	130	100	116	120	116	125	119	123	115	3.6
8	100	90	135	100	112	114	105	133	119	130	114	4.8
9	100	86	141	100	108	114	95	125	119	130	112	5.4
10	106	81	123	100	108	118	79	125	115	130	109	5.6
15	93	90	94	100	108	100	79	119	100	115	100	3.8
20	93	95	94	112	125	89	79	119	92	107	101	4.6
25	100	109	117	125	137	95	84	119	92	123	110	5.4
30	112	115	117	125	145	105	100	120	100	150	119	5.4
35	125	122	132	126	141	105	100	120	103	169	124	6.5
40	137	127	111	126	125	107	111	120	103	184	125	7.3
45	137	127	100	125	104	100	111	121	105	169	120	6.8
50	100	127	94	125	95	100	111	121	104	169	115	7.2
55	100	131	105	125	97	100	100	122	103	176	116	7.7
60	112	131	123	125	100	95	111	129	101	184	121	8.1
65	114	131	108	125	106	95	105	133	101	184	120	8.2
70	114	128	110	145	106	100	100	121	101	184	121	8.4
75	115	122	114	147	102	100	103	125	101	184	121	8.4
80	116	127	123	150	100	100	103	125	103	184	123	8.4
85	115	125	128	150	91	102	111	125	103	184	123	8.5
90	118	122	137	150	93	102	113	125	103	184	125	8.5

TABLE II

INTRACRANIAL PRESSUE OF THE HIGH-DOSE GROUP

Monkey No.	11	12	13	14	15	16	17	18	19	20	Mean	S.E.
Pre-exposure Pressure ($cm\ H_2O$)	5.5	14.0	3.0	9.5	4.0	5.0	4.0	2.5	3.0	3.75	5.43	
Minutes Postexposure	Percentage of Pre-exposure Pressure											
1	100	100	100	103		100	100	100	100	100	100	0.3
2	100	100	100	105	100	100	100	100	100	100	101	0.5
3	100	100	100	105	113	100	100	100	100	100	102	1.4
4	131	107	200	121	113	160	100	100	183	133	135	11.7
5	173	150	267	153	138	220	75	100	267	213	176	21.8
6	218	136	217	168	163	200	75	100	417	200	189	31.8
7	200	157	200	158	169	160	50	100	300	133	163	22.0
8	182	139	167	147	163	130	100	100	167	100	140	10.4
9	145	138	167	137	138	120	125	100	133	67	127	9.1
10	118	132	167	132	125	100	150	100	133	67	122	9.4
15	64	79	83	97	113	60	150	100	100	107	95	8.7
20	55	64	100	116	113	55	150	50	117	120	94	11.7
25	45	64	133	100	138	50	175	50	133	133	102	15.6
30	45	75	150	105	119	50	175	50	135	160	105	16.1
35	64	93	200	105	163	44	175	80	133	213	127	19.6
40	55	104	233	105	175	48	175	80	133	200	131	21.0
45	59	114	167	105	200	100	250	100	117	207	142	20.2
50	64	107	200	105	200	90	250	120	100	213	145	21.4
55	68	114	208	107	250	90	213	120	117	227	151	21.9
60	82	100	217	111	263	90	213	120	100	200	150	22.0
65	91	96	267	105	275	100	200	140	117	187	158	23.5
70	91	89	275	111	281	110	188	160	133	173	161	23.4
75	82	75	283	105	313	120	188	160	100	240	167	28.7
80	77	75	300	105	350	125	188	160	100	267	175	32.9
85	73	75	300	111	350	125	213	160	100	240	175	32.4
90	77	75	317	111	350	130	225	200	100	213	180	32.7

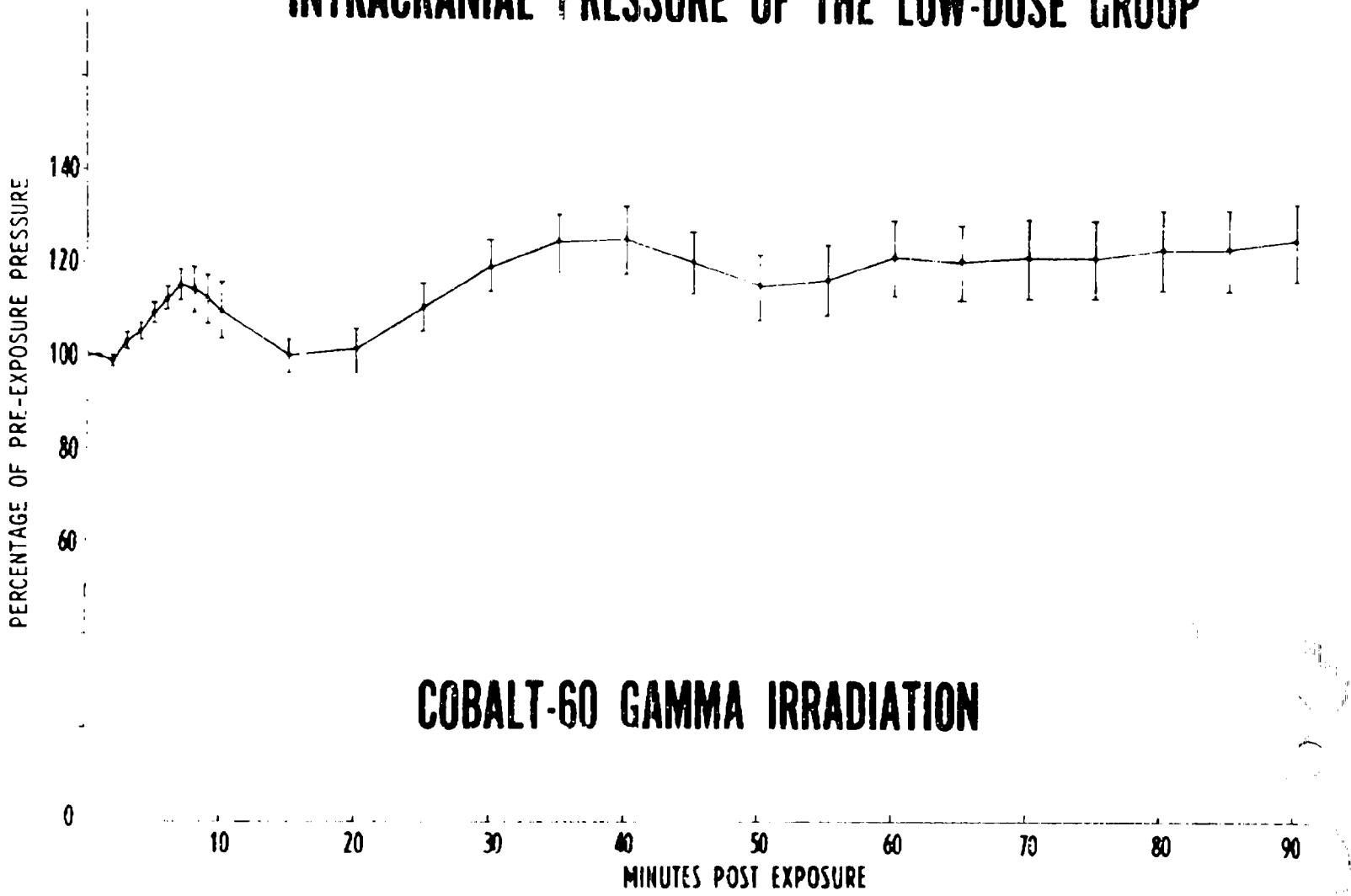

FIGURE 3 - THE AVERAGE RESPONSE OF ICP IN 10 MONKEYS EXPOSED TO 1307 RAD (MID-THORAX) OF COBALT-60 IRRADIATION. STANDARD ERROR OF THE MEAN PLOTTED FOR EACH DATA POINT.

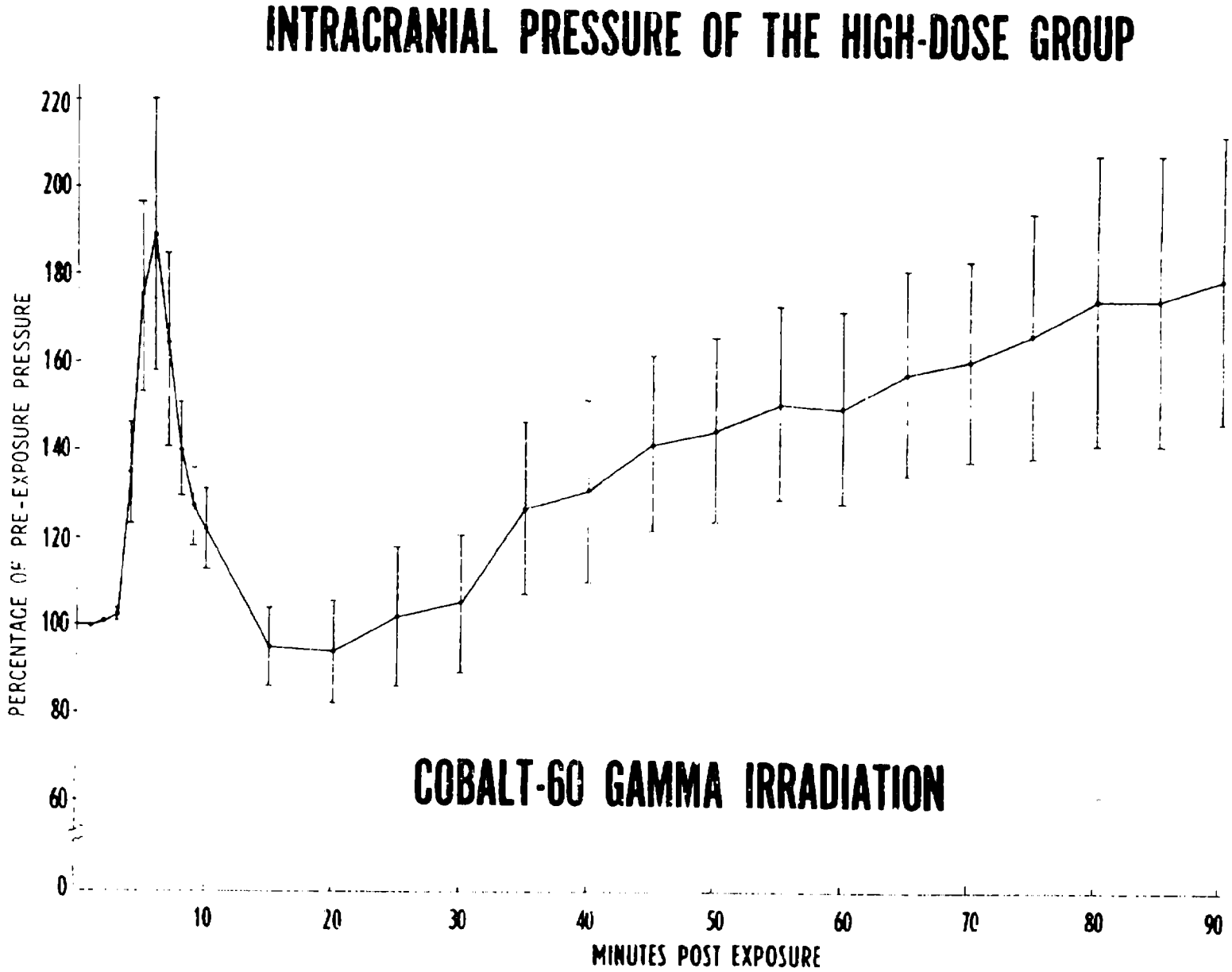

FIGURE 4 - THE AVERAGE RESPONSE OF ICP IN 10 MONKEYS EXPOSED TO 2244 RAD (MID-THORAX) OF COBALT-60

Figure 5 illustrates the relationship of the average ICP response observed in both exposure groups. The low-dose group was tested at 7 minutes postexposure and at 90 minutes by use of Student's T-Test, which indicated the values were significantly different than baseline values. The high-dose group was also significantly different from baseline recordings at 6 minutes and 90 minutes postexposure. Tests performed 6 minutes, 7 minutes, and 90 minutes indicated that responses between the two groups were significantly different at the first 2 times periods but not for the 90 minutes postexposure times.

The blood pressure response of each animal is listed in Tables III and IV. The low-dose group demonstrated maximum hypotention within 10 minutes after irradiation, as illustrated in Figure 6. The blood pressure gradually returned to the preirradiated level at 30-minutes postexposure, and then declined to 95% of baseline within the next hour; however, when tested at the 5% level, the 95% value was not significantly different from baseline.

The blood pressure of the high-dose group began a precipitous decline 2 minutes after the initiation of irradiation (Figure 7), and maximum hypotension was reached at 10 minutes postexposure; afterwhich, pressure began a gradual rise but did not attain baseline value by the end of 90 minutes.

When the nadir of both groups was statistically evaluated at 10 minutes postirradiation, both differred significantly from baseline. Differences between the two groups at 10 minutes postirradiation were significantly different, but not at 90 minutes following exposure.

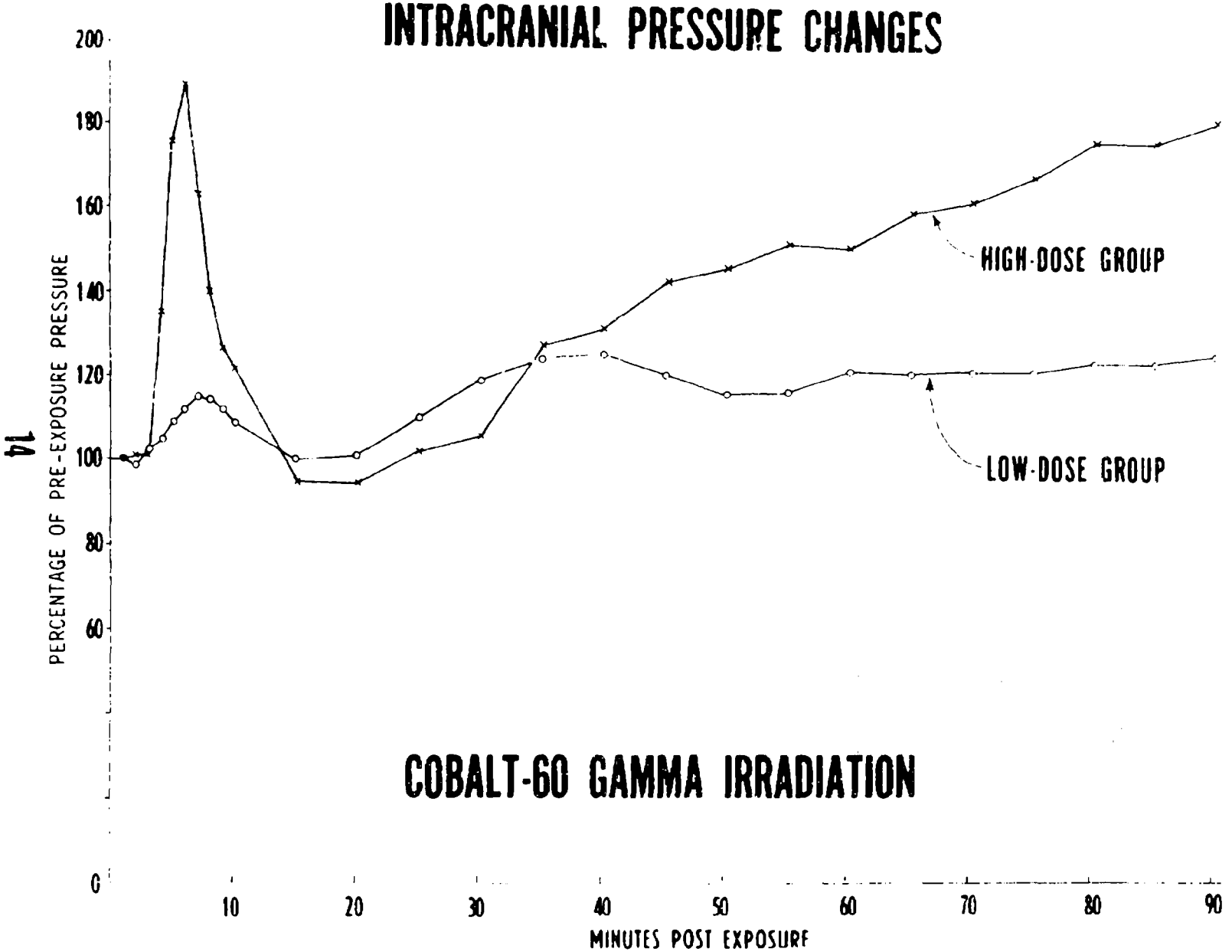

FIGURE 5 - A COMPARISON OF THE AVERAGE ICP RESPONSE

TABLE III

ARTERIAL BLOOD PRESSURE OF THE LOW-DOSE GROUP

Monkey No.	1	2	3	4	5	6	7	8	9	10	Mean	S.E.
Pre-exposure Pressure (mm Hg)	90	95	100	92	90	90	105	90	85	80	92	
Minutes Postexposure	Percentage of Pre-exposure Pressure											
1	100	100	100	100	100	100	100	100	100	100	100	0.0
2	100	100	95	100	100	100	100	100	100	100	99	0.5
3	100	100	95	100	115	100	100	100	100	100	101	1.7
4	100	100	90	103	120	102	95	100	103	100	101	2.6
5	100	110	75	103	118	111	85	100	105	98	101	4.2
6	94	110	62	103	109	106	81	100	105	95	96	4.9
7	91	110	65	103	100	97	76	109	98	88	94	4.8
8	91	105	68	103	96	86	64	111	89	81	89	5.1
9	88	105	70	103	96	72	62	117	76	75	86	6.1
10	88	100	65	103	96	67	57	117	75	75	84	6.5
15	88	97	77	105	103	59	55	111	71	84	85	6.5
20	88	94	72	114	111	78	62	123	68	94	90	6.9
25	96	97	67	114	124	83	62	123	68	103	94	7.7
30	100	101	65	114	133	103	76	123	72	116	100	7.6
35	100	100	59	113	123	111	95	123	74	118	102	7.1
40	100	98	65	108	118	102	90	117	75	125	100	6.3
45	100	106	68	103	100	109	74	114	75	113	96	5.7
50	94	111	65	102	96	107	70	107	75	110	94	5.8
55	94	105	70	102	104	100	69	107	77	106	93	5.1
60	94	107	75	102	104	94	69	100	77	113	94	5.0
65	96	105	86	110	110	104	69	100	77	113	97	5.0
70	96	100	83	113	107	104	78	100	81	115	98	4.4
75	98	96	75	111	104	100	78	102	82	115	96	4.5
80	98	104	73	109	104	100	78	102	83	115	97	4.6
85	95	97	80	108	101	90	79	102	83	115	95	4.0
90	95	97	82	108	101	84	81	102	85	115	95	3.9

TABLE IV

ARTERIAL BLOOD PRESSURE OF THE HIGH-DOSE GROUP

Monkey No.	11	12	13	14	15	16	17	18	19	20	Mean	S.E.
Pre-exposure Pressure (mm Hg)	80	100	100	105	95	82	95	90	95	93		
Minutes Postexposure	Percentage of Pre-exposure Pressure											
1	100	100	100	100	100	100	100	100	100	100	100	0.0
2	100	100	100	100	100	100	100	100	100	100	100	0.0
3	88	100	100	90	100	98	100	100	98	97	97	1.4
4	70	90	85	83	105	88	100	100	78	89	89	3.4
5	58	85	70	79	103	104	100	98	76	89	86	4.9
6	53	65	37	76	105	79	95	98	56	74	74	6.8
7	53	50	37	54	105	73	95	96	48	68	68	7.5
8	65	47	37	43	98	63	95	96	41	65	65	7.5
9	70	50	37	38	84	61	95	96	39	71	64	7.2
10	74	50	40	38	74	59	95	92	39	74	64	6.8
15	74	63	42	43	74	55	89	89	44	81	65	5.9
20	79	67	42	52	84	63	89	100	50	95	72	6.4
25	82	90	47	62	89	71	89	100	56	105	79	6.1
30	88	90	45	59	95	76	89	100	56	105	80	6.5
35	88	87	50	67	100	77	89	100	56	100	81	5.8
40	88	85	67	71	95	85	95	100	67	100	85	4.1
45	88	87	70	74	95	91	95	100	67	100	87	3.9
50	93	85	75	78	95	91	105	100	67	100	89	3.9
55	93	85	82	78	89	94	116	100	67	100	90	4.3
60	93	85	82	78	89	94	116	100	70	100	91	4.1
65	109	83	85	80	97	98	121	103	70	95	94	4.8
70	114	83	83	80	100	101	116	103	70	100	95	4.8
75	109	80	85	80	84	104	116	103	67	95	92	4.9
80	105	75	83	80	93	104	116	103	61	95	92	5.3
85	100	73	85	76	93	104	116	103	61	95	91	5.4
90	88	70	80	76	93	106	116	103	61	95	89	5.4

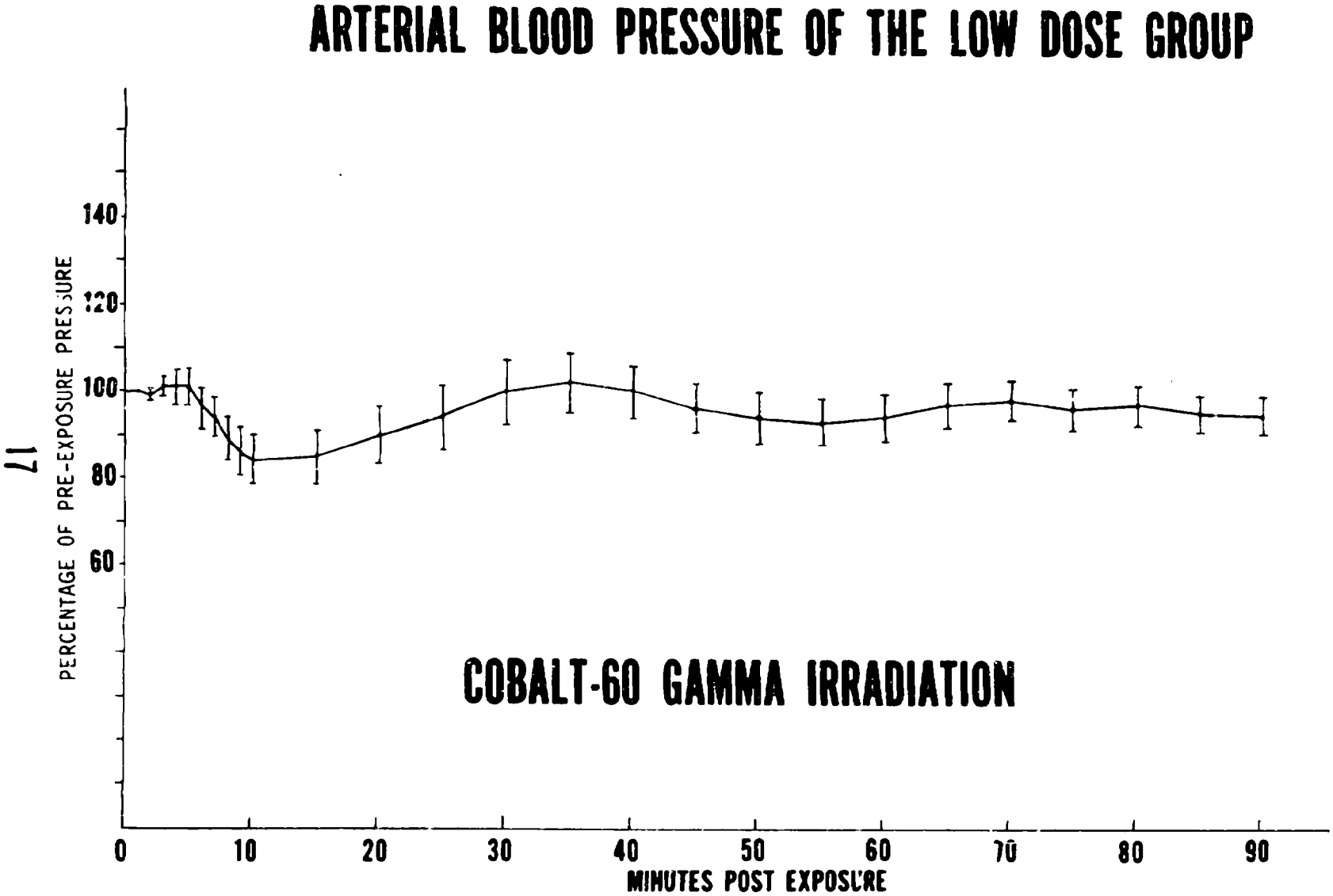

FIGURE 6 - THE AVERAGE RESPONSE OF ARTERIAL BLOOD PRESSURE IN 10 MONKEYS EXPOSED TO 1307 RAD

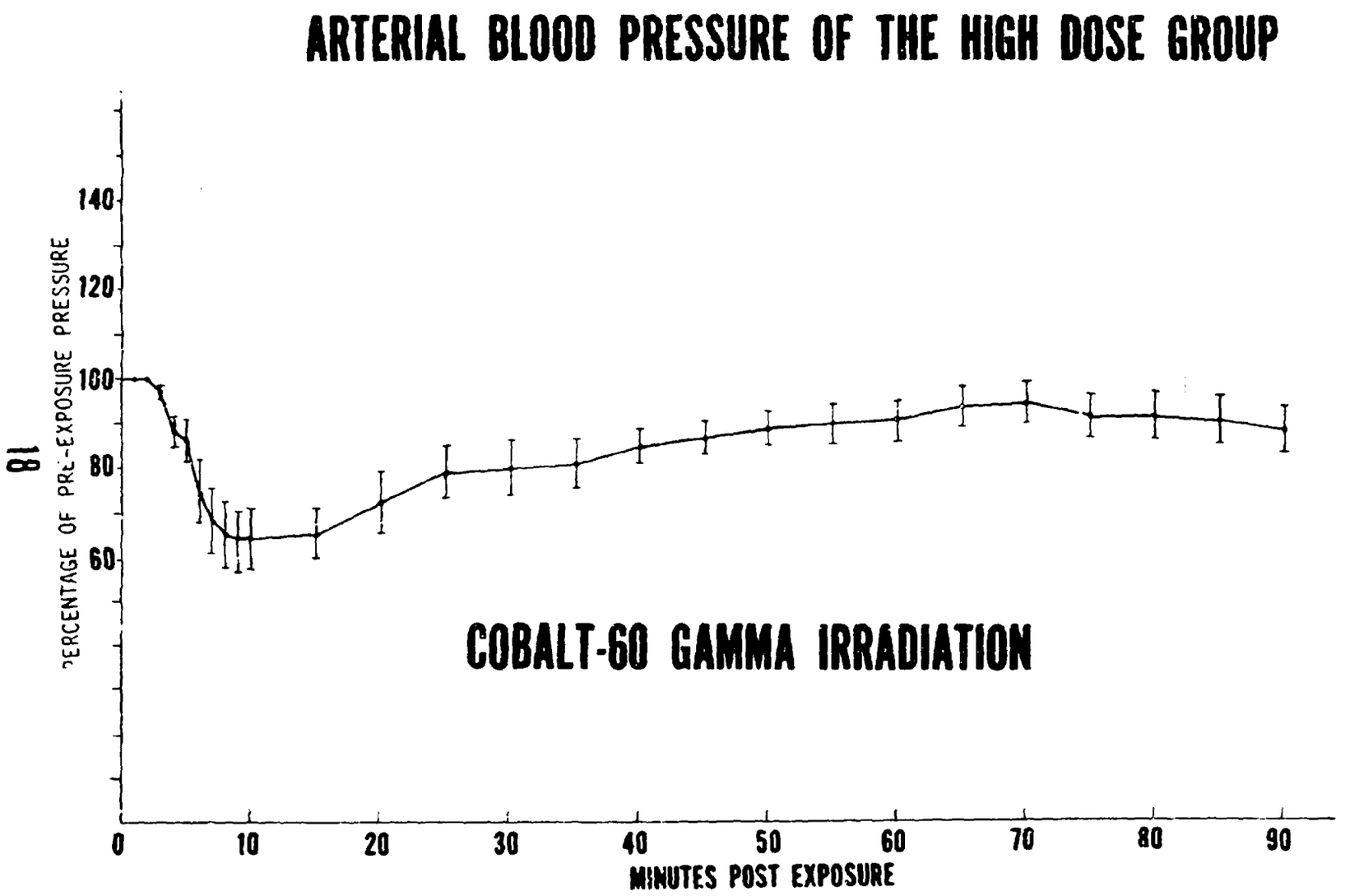

FIGURE 7 - THE AVERAGE RESPONSE OF ARTERIAL BLOOD PRESSURE IN 10 MONKEYS EXPOSED TO 2244 RAD OF COBALT-60

Figure 8 illustrates the average blood pressure response of both groups. Correlation of ICP and blood pressure responses observed in both groups are illustrated in Figures 9 and 10. The ICP and blood pressure fluctuated in harmony beginning approximately 20 minutes postirradiation for the low-dose group, but the ICP of the high-dose group demonstrated a much greater rate of increase than was observed for the blood pressure.

Tissue-equivalent monkey phantoms were used to measure absorbed doses in the head, thorax, and abdominal area; however, due to the great discrepancy between this dosimetry and the measured doses on the individual animals, it was felt that more confidence could be placed in results of the individual dosimetry. Listed in Table V are the entry and exit doses as well as the calculated midline doses for each monkey. Since electronic equilibrium was not established in the surface (entry) dosimeters, the mid-line exposures were calculated from the exit doses. It has been shown that calculated exposures for the chest region may be off by 25-30% if corrections are not made for the air-filled lungs[11].

The monkeys used in this project had average chest measurements of approximately 8 cm from side-to-side. The inverse square law was applied to the exit measurements to derive the estimated mid-thoracic absorbed dose values in rad. It is conceded that such calculations will be slightly higher than the actual exposure level due to tissue absorption. But, without knowing the exact ratio of tissue to air within the thorax at the time of irradiation, it is not possible to establish an accurate absorption coefficient.

11. V. Svarcer, J.F. Fowler, T.J. Deeley, E. Shuttleworth, Exit doses for lung and pharynx treatment fields measured by lithium fluoride thermoluminescence. Luminescence Dosimetry, (International Conference on Luminescence Dosimetry, U.S. Atomic Energy Commission/ Division of Technical Information. June 1965).

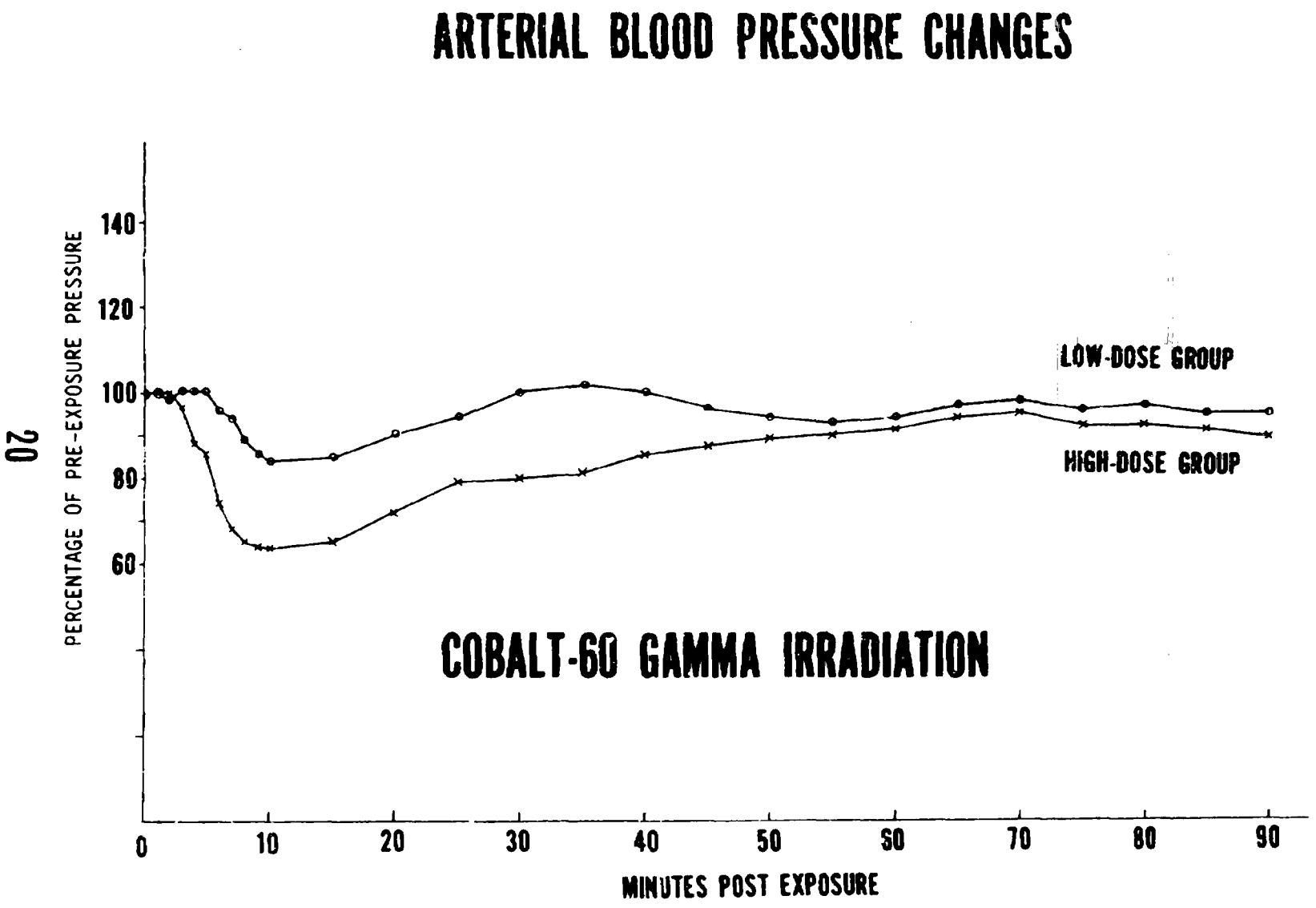

FIGURE 8 - A COMPARISON OF THE AVERAGE BLOOD PRESSURE RESPONSE OBSERVED BETWEEN THE LOW AND HIGH-DOSE GROUPS.

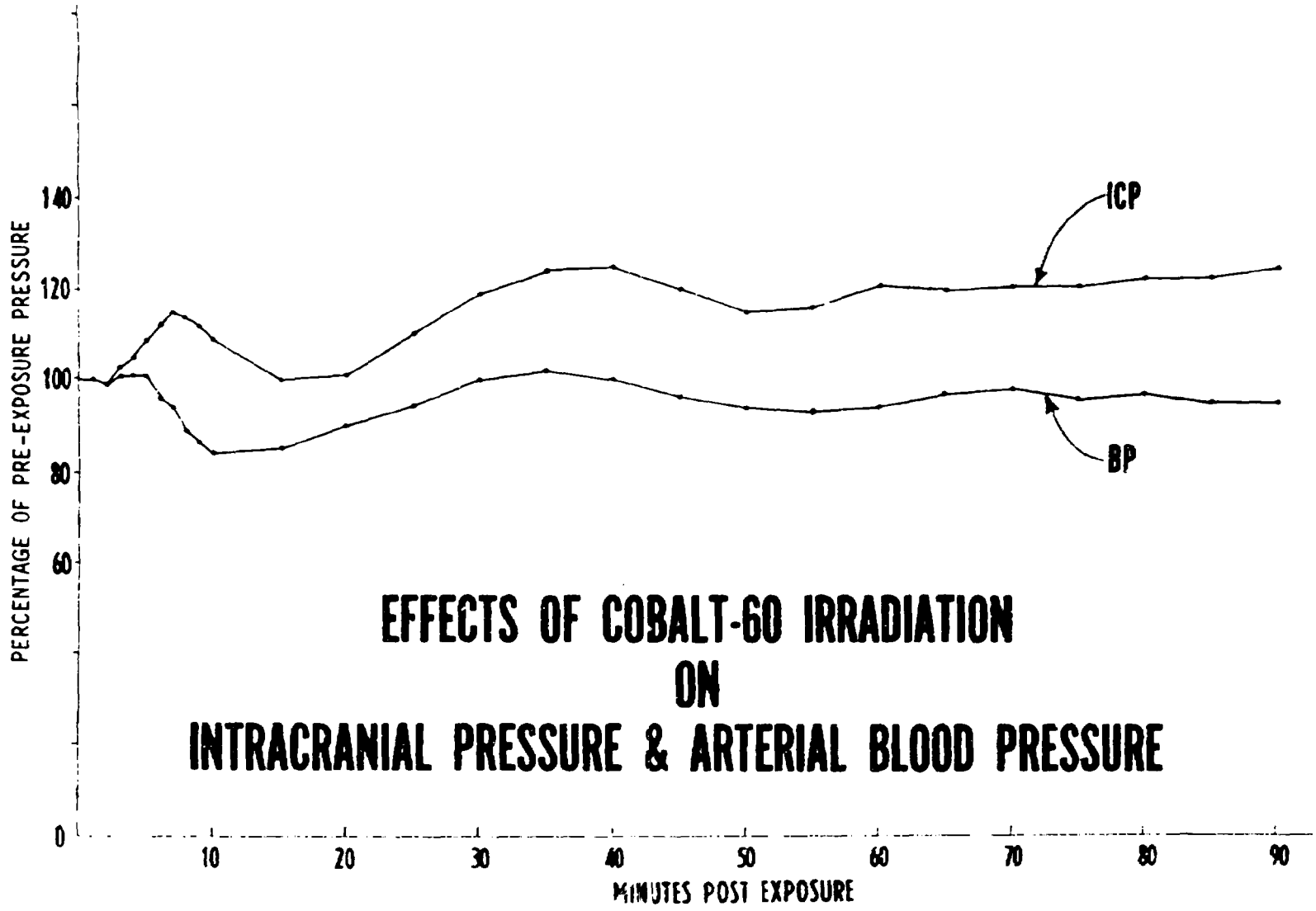

FIGURE 2 - AN ILLUSTRATION OF THE AVERAGE ICP AND BLOOD PRESSURE OBSERVED IN 10 MONKEYS EXPOSED TO 1307 RAD (MID THORAX) OF COBALT-60 GAMMA

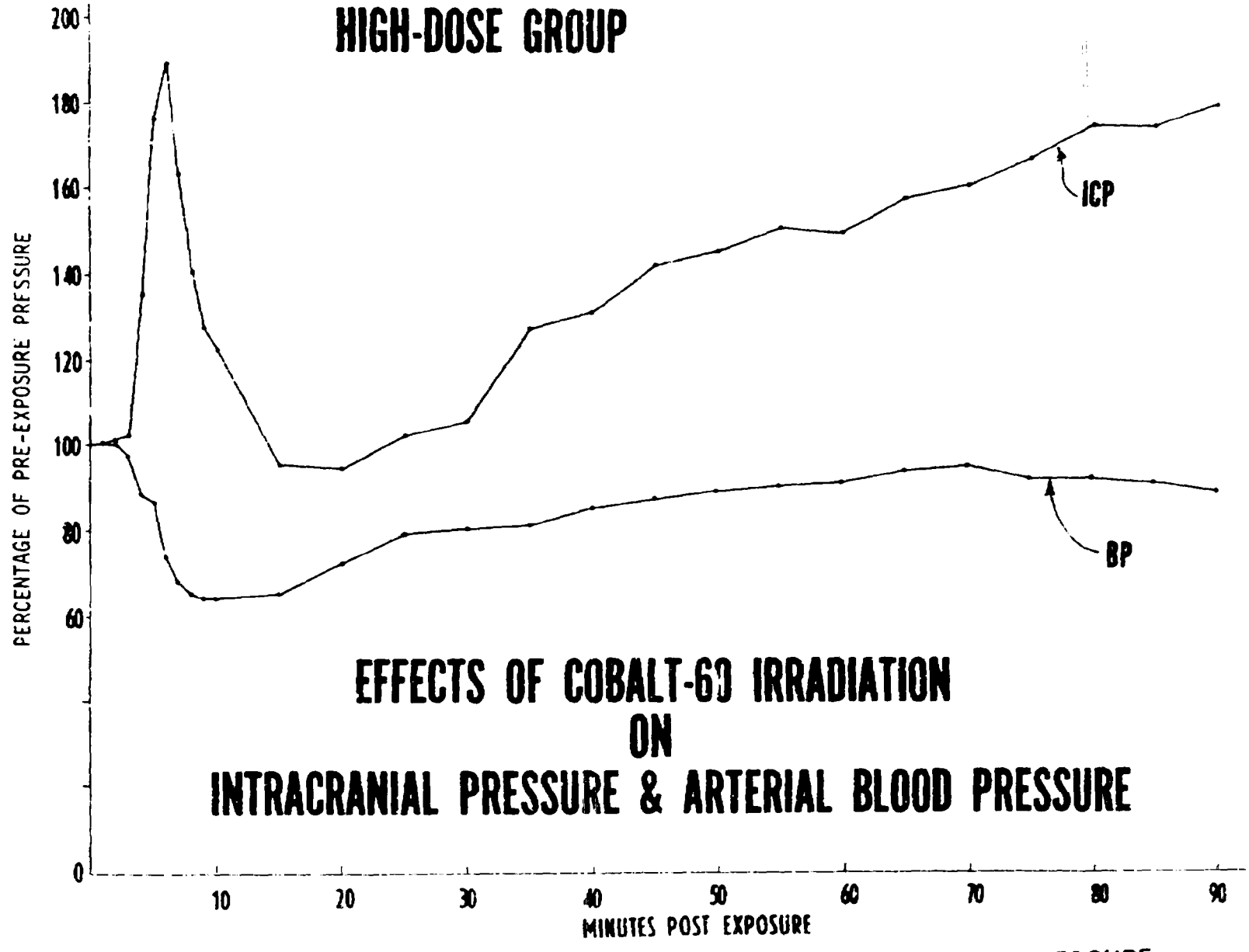

FIGURE 10 - AN ILLUSTRATION OF THE AVERAGE ICP AND BLOOD PRESSURE

TABLE V

LOW DOSE GROUP

Monkey No.	Weight in kg.	Entry dose in rad	Exit dose in rad	Exit Dose / Entry dose x 100	Calculated average mid-thoracic dose
1	3.1	2328	1052	45	1210
2	3.4	2785	1128	41	1297
3	2.6	2640	1223	46	1406
4	2.8	2611	1215	47	1397
5	2.8	2643	1018	39	1171
6	2.8	2723	1156	42	1329
7	2.2	2428	1185	49	1363
8	2.3	2275	1053	46	1211
9	3.0	2841	1305	46	1501
10	2.6	2305	1033	45	1188
	2.8	2558	1137	45	1307

HIGH DOSE GROUP

11	3.8	4204	1852	44	2130
12	4.0	4019	1950	49	2243
13	4.0	4113	1869	45	2149
14	4.0	4564	2039	45	2345
15	4.7	4418	1942	44	2233
16	4.0	4766	2064	43	2374
17	2.8	4049	1729	43	1988
18	3.2	4303	1941	45	2232
19	3.0	4633	2009	43	2310
20	3.8	4642	2120	46	2438
	3.7	4371	1952	45	2244

DISCUSSION

The low-dose group demonstrated a slight, although not significant, rise in the blood pressure at approximately 3 minutes from the beginning of the exposure; this period corresponds to the time at which the ICP is beginning to elevate. This fact indicates that perhaps the intracranical vessels are beginning to dilate and that the ICP is increasing because the arterial pressure has not yet begun to fall. The arterial pressure begins to diminish at approximately 6 minutes and reaches the nadir at 10 minutes. Note that the ICP has begun to decrease while the blood pressure is still falling. This fact may suggest that the intracranial vessels have reached maximum dilation and that the ICP then begins to follow the blood pressure fluctuations. At the end of the 90-minute observation period, the blood pressure had returned to 95% of baseline, and the ICP was 125% of baseline.

The ICP and blood pressure of the high-dose group began to change at 3 minutes after the initiation of irradiation as compared to 6 minutes observed in the low-dose group. Although the pressure responses are more rapid and of greater magnitude in the high-dose group, the general trend is the same; for example, the ICP reaches maximum response and begins to decrease during the time period in which the arterial pressure is falling. At 20-minutes postirradiation the ICP begins to increase for the second time and continues to rise without regard to the blood pressure response. Ninety-minute postexposure, the arterial pressure was 84% of baseline and the ICP was 165% of the preirradiation value. It might be concluded that in the high-dose group there has been more capillary damage and increased vessel permeability that could account for a shift in the perivascular osmotic pressure. There does appear to be two separate mechanisms affecting the intracranial pressure at different

periods of time after exposure to high doses of whole body irradiation.

The intracranial pressure increase observed an hour postirradiation may be indicative of brain edema and breakdown of the capillary integrity, but this fact does not account for the change in behavioral patterns that occur a few minutes postirradiation. It is doubtful that 75-80% increase in ICP is sufficient to induce severe cerebral dysfunction. The increase in ICP during the early stages of hypotension suggests dilation of the intracranial vessels and thereby an increase in the brain blood flow. However, there is a short period of time when both ICP and blood pressure are decreased, a period when brain ischemia could occur. At the present time this is the only explanation offered for the radiation induced cerebral depression.